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SUBJECT: Systemic Toxicity Review of [redacted] P08-88)

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[redacted]

I. CONCLUSIONS

In the SAT report on P08-88, there is concern for liver, kidney, and blood effects based on the submitted toxicity data and concern for lung effects if inhaled based on the surfactant properties of the PMN compound.

The studies reviewed below adequately meet TSCA requirements for acute oral toxicity and 28-day oral toxicity testing with P08-88. The acute oral LD_{50} is consistent with a low degree of toxicity. A no-observable-adverse-effect level (NOAEL) of 5 mg/kg/day in the 28-day oral toxicity study based on signs of kidney and liver toxicity at higher dose levels is concluded. Effects on blood were not determined in this study.

Systemic toxicity data with various analogs also show liver and kidney as target organs. Toxic signs in other target organs in the analog data were not found in the 28-day study with P08-88. Irritation found in skin irritation studies with analogs support P08-88 as a potential irritant to skin and probably eye.

If a more robust systemic toxicity assessment of P08-88 is desired, considering the

broader findings of toxicity, including reproductive tissues, in the analog data, OECD guideline 422 with oral dosing is proposed. If lung effects are of concern based on the statement in the SAT report, the inhalation exposure route can be substituted for this study. Based on irritation data with analogs, irritation studies (OECD guidelines 404 (skin) and eye (405)) with P08-88 are recommended

II. BASIS FOR CONCLUSIONS

The PMN test substance, [redacted], water solubility described as dispersible, and vapor pressure below 0.045 torr at 25 °C (SAT Report).

In the study reports, the PMN test substance is described [redacted].

Predicted absorption of P08-88 is good through lung and gastrointestinal tract, nil through skin as neat material, and poor through skin when in solution (SAT Report).

The analog [redacted] water solubility described as dispersible, and vapor pressure below 0.0325 torr. Test agent purity was [redacted] (SAT Report).

The analog in [redacted] test data was [redacted].

The analog [redacted] described as dispersible, and negligible vapor pressure (Submission and SAT Report). The test substance is identified as [redacted] except in the acute oral toxicity study in which the test substance is identified as [redacted] and the 28-day and 90-day oral toxicity studies in which purity of the test substance is reported [redacted] (Submission).

The analog perfluorooctanoic acid (CAS No. 335-67-1) is a solid with a molecular weight of 414, water solubility of 3.4 g/L, and vapor pressure of 10 mm Hg at 25 °C (2005 USEPA Draft Risk Assessment on PFOA).

1. Systemic Toxicity Tests with P08-88

a. Acute Oral Toxicity Study in Rats

This study is consistent with OECD guideline 423. Three female Crl:CD (SD) IGS BR rats were given 2,000 mg/kg and 6 female rats were given 300 mg/kg of test substance in distilled water. Dosing was by gavage. Animals were sacrificed on day 14 post-treatment and were observed for survival, clinical signs, body weight, and gross pathology.

No deaths occurred with 300 mg/kg. All animals given 2,000 mg/kg died within 1 day of treatment. The acute oral LD_{50} was between 300 and 2,000 mg/kg.

Clinical signs in decedents included hunched posture, lethargy, ataxia, decreased and noisy respiration, diuresis, and dehydration. Survivors showed no clinical signs.

Body weight was normal in survivors.

Gross pathology was unremarkable in survivors. In decedents were found abnormally red lungs, dark liver, and dark kidneys.

Because 300 mg/kg which did not cause death is close to 500 mg/kg which is the lowest dose in the OPPT criteria for low acute oral toxicity and 2,000 mg/kg is well above 500 mg/kg, the acute oral LD_{50} is concluded consistent with low acute oral toxicity.

b. Twenty Eight-Day Oral Toxicity Study in Rats

This study is consistent with OECD guideline 407, and dose levels were based on a 14-day oral dose toxicity study. Five male and 5 female Crl:CD (SD) rats per group were given 0 (vehicle control), 5, 25, or 100 mg/kg/day of test substance in purified water by gavage daily for 28 days with terminal sacrifice on day 29. Additional groups of 5 males and 5 females per group were similarly treated with 0 (vehicle controls) or 100 mg/kg/day and sacrificed after 14 days of recovery. Rats were 5 weeks old at the start of the study. The rats were evaluated for survival, functional observational battery, motor activity, clinical signs, body weight, food consumption, hematology, clinical chemistry, urinalysis, gross pathology, organ weights, and histopathology.

All animals survived.

In hematology, prothrombin time and reticulocytes were increased in males and females given 100 mg/kg/day, respectively.

In clinical chemistry, alanine aminotransferase (ALT) and albumin/globulin ratio were increased in males given 100 mg/kg/day, ALT was increased in treated recovery males, cholesterol was decreased in males given 100 mg/kg/day, and bilirubin was decreased in females given 100 mg/kg/day

Absolute and relative (organ/body) kidney weights were increased in males given 25 or 100 mg/kg/day and in treated recovery females, absolute and relative liver weights were increased in males given 100 mg/kg/day, and relative adrenal weights were increased in males given 100 mg/kg/day.

In gross pathology, there were elevation of the limiting ridge of the forestomach in 4 males and 1 female given 100 mg/kg/day and enlarged liver in 2 males given 100 mg/kg/day.

In histopathology, there were squamous cell hyperplasia in the limiting ridge of the forestomach in both sexes given 100 mg/kg/day, diffuse hypertrophy of hepatocytes with granular degeneration in liver of males given 100 mg/kg/day, focal necrosis of hepatocytes in liver in 1 female given 100 mg/kg/day, tubular cell epithelium hyperplasia in kidney in 1 female given 100 mg/kg/day, and a solitary cyst in kidney medulla in 1 male given 100 mg/kg/day

Other findings were unremarkable.

Based on increases in absolute and relative kidney weights in males at higher dose levels, the investigators concluded a NOEL of 5 mg/kg/day. This conclusion is acceptable as a NOAEL. In clinical chemistry and pathology, signs of kidney, liver, and forestomach toxicity were found in animals given 100 mg/kg/day.

2. Systemic Toxicity Tests with [redacted]

Discussion of systemic toxicity tests is from the SAT report [redacted]

a. Skin Irritation Study in Rabbits

This study was based on OECD guideline 404. Onto skin clipped free of fur was applied 0.5 g of test agent to each of 3 New Zealand white rabbits under semi-occlusive dressing. Exposure was 4 hours. Animals were observed for 72 hours post-treatment, and skin irritation was scored by the Draize method.

Well-defined erythema, slight edema, blanching, and slight or severe desquamation at test sights were observed. The Draize score was 4.

By Draize criteria, the test substance was a moderate irritant in this study.

b. Eye Irritation Study in Rabbits

This was an in vitro test without an OECD guideline. Onto each of 3 enucleated eyes from rabbits was applied 0.1 ml of test substance. Two eyes treated with saline served as controls. Eyes were maintained in a superfusion chamber before treatment. Corneal thickness was measured before enucleation, after equilibration, and for 4 hours following treatment.

After 60, 120, and 240 minutes of observation, 23.4, 28.5, and 49.1 % corneal swelling was found, respectively, in treated eyes.

The test agent was concluded to be a potentially severe eye toxicant from results of this study. Apparently, positive controls were not done or reported to support validity of this test for eye irritation potential. Because this technique is not an eye irritation test per OECD or OPPTS guidelines, applicability of these results to hazard assessment is questionable. Confirmation of these results with an eye irritation test done by OECD guideline 405 is recommended.

c. Acute Oral Toxicity Study in Rats

This study is consistent with OECD guideline 423. Three female Sprague-Dawley CD rats were given 2,000 mg/kg and 6 female rats were given 300 mg/kg of test substance in distilled water. Dosing was by gavage. Animals were sacrificed on day 14 post-treatment and were observed for survival, clinical signs, body weight, and gross pathology.

No deaths occurred with 300 mg/kg. All animals given 2,000 mg/kg died. The acute oral LD_{50} was between 300 and 2,000 mg/kg.

Clinical signs in decedents included hunched posture, lethargy, ataxia, decreased and labored respiration, diuresis, piloerection, and hypothermia. Survivors showed no clinical signs.

Body weight was normal in survivors.

Gross pathology was unremarkable in survivors. In decedents were found abnormally red lungs, dark liver, and dark kidneys.

Because 300 mg/kg which did not cause death is close to 500 mg/kg which is the lowest dose in the OPPT criteria for low acute oral toxicity and 2,000 mg/kg is well above 500 mg/kg, the acute oral LD_{50} is concluded consistent with low acute oral toxicity.

3. Systemic Toxicity Tests with the Analog in [redacted].

This 8e submission is short paragraph summaries of the following test data. These studies should be considered provisional until complete reports, if available (they were done during the 1960s), are provided.

Single gavage treatment of rats with 12 mg/kg test substance induced abnormal liver pathology (hepatomegaly, hepatocyte hypertrophy, vacuolation, isolated cell necrosis) and reduced pentobarbital sleeping time, an indicator of altered metabolism.

Repeated dose gavage treatment with 0.6 mg/kg/day of test agent in rats for 2 weeks caused similar toxic signs in liver.

An approximate lethal dose of 130 mg/kg with similar liver injury occurred in rabbits acutely treated dermally.

In dogs given acute gavage doses of 4 - 60 mg/kg of test substance, serum enzyme changes and cholesterol levels in clinical chemistry suggested liver injury. However, pathology was not assessed, dose response cannot be determined as reported, and there were no controls.

There is consistent evidence of liver toxicity at low dose levels, but this 8e submission is too brief to allow review of the data.

4. Systemic Toxicity Tests with [redacted]

a. Acute Oral Toxicity Study in Rats

This study is consistent with OECD guideline 423. Three male and 3 female Hsd: Sprague-Dawley SD rats per group were given test substance by gavage at doses of 2,000 or 200 mg/kg. Test material formulation was diluted as needed with distilled water to achieve desired doses. Animals were sacrificed on day 14 post-treatment and were observed for survival, body weights, clinical signs, and gross pathology.

All animals survived except 2 females given 2,000 mg/kg. The acute oral LD_{50} was above 2,000 mg/kg in males and between 2,000 and 200 mg/kg in females.

Clinical signs included piloerection, reduced activity, ataxia, and liquid feces in survivors and soft feces, unconsciousness, ataxia, lethargy, piloerection, hypothermia, pallor, and swollen abdomen in decedents.

Body weight gain appeared normal.

Abnormalities found in gross pathology were multiple dark areas in kidneys, lungs, or thymus in 2 males given 200 mg/kg.

Considering survival of all animals given 200 mg/kg, which is rather close to the 500 mg/kg criterion for low acute oral toxicity by OPPT, and the survival of all males and 1 female given 2,000 mg/kg, which is well above 500 mg/kg, the acute oral LD_{50} estimates in this study are concluded to be consistent with low acute oral toxicity.

b. Dermal Irritation Study in Rabbits

This study is consistent with OECD guideline 404. Onto intact skin clipped free of fur of each of 3 female New Zealand albino rabbits was applied 0.5 g of test material as a paste in 0.3 ml of sterile water under semi-occlusive dressing. Exposure to test substance was 4 hours. Irritation scored according to the Draize method during 3 days following treatment.

Well-defined erythema and very slight to slight edema were observed at 1 hour post-treatment, and very slight edema was observed at 1 day post-treatment. Test site reactions resolved by 2 days post-treatment. The maximum mean Draize score was 2.3.

By Draize criteria, the test agent was moderately irritating in this study. Considering the maximum Draize score of 2.3 as close to the margin between slightly (2.0) and moderately (2.1) irritating by Draize criteria and reversibility of skin reactions by 2 days post-treatment, results are concluded to support low concern for dermal irritation by the test substance.

c. Acute Dermal Toxicity Study in Rats

This study is consistent with OECD guideline 402; however, this study was a limit test since only 1 dose was used. Onto intact skin clipped free of fur of each of 5 male and 5 female Hsd: Sprague-Dawley rats was applied 2,000 mg/kg of test material as a paste in 0.5 ml of sterile water under semi-occlusive dressing. Exposure to test substance was 24 hours. Animals were observed for survival, clinical signs, and gross pathology through terminal sacrifice on study day 15.

All animals survived. The acute dermal LD_{50} was above 2,000 mg/kg.

Results were unremarkable except for emaciation and body weight reduction.

Results of this study support low acute dermal toxicity by the test material.

d. Fourteen-Day Oral Toxicity Study in Rats

This study is consistent with OECD guideline 407, but the study was 14 days rather than 28 days. Five male and 5 female HanBrl:WIST (SPF) rats per group were given 0 (vehicle control), 10, 50, or 250 mg/kg/day of test substance in bidistilled water by gavage daily until terminal sacrifice at the end of the 14-day study. Rats were 7 weeks old at the start of treatment. Rats were evaluated for survival, clinical signs, body weight, food consumption, functional observational battery, motor activity, hematology, clinical chemistry, gross pathology, organ weights, and histopathology. Because of mortality patterns, hematology and clinical chemistry data was not obtained in the decedents noted below.

All control animals, all animals given 10 mg/kg/day, and 2 males given 50 mg/kg/day survived. Remaining animals died before terminal sacrifice. Females given 50 mg/kg/day died on study day 13, and animals given 250 mg/kg/day died by study day 6.

In the functional observational battery, females given 50 mg/kg/day experienced ataxia, stiff gait, tremor/twitching, and prostration. Both sexes given 50 mg/kg/day displayed lower grip strength of forelimbs and hindlimbs and reduced locomotor activity. Females given 10 mg/kg/day had slightly reduced hindlimb grip strength.

Clinical signs included piloerection, hunched posture, sedation, emaciation, and dyspnea in rats given 50 mg/kg/day.

Body weights were lower in both sexes in all treated groups, and food consumption was lower in both sexes given 50 or 250 mg/kg/day.

In hematology, effects in all treated animals included reduced platelet counts, shorter mean thromboplastin time, shorter activated partial thromboplastin time (although prolonged in males given 10 mg/kg/day), reduced mean corpuscular volume, reduced mean reticulocyte counts. In males given 50 mg/kg/day, monocyte counts, red cell volume distribution, and hemoglobin concentration distribution were increased

In clinical chemistry, effects in all treated animals included increases in glucose, urea, alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, chloride, and albumin/globulin ratios, glutamate dehydrogenase (males given 50 mg/kg/day and females), and alkaline phosphatase (females only) and decreases in cholesterol, phospholipid, triglycerides (males only), creatinine, total protein, albumin (males only), globulin, calcium, and inorganic phosphate (males given 50 mg/kg/day only).

In all surviving treated animals, absolute and relative (organ/body) liver weights were increased and absolute and relative weights of adrenals, thymus, and spleen were decreased. Absolute and relative weights of testes and epididymides were reduced in males given 50 mg/kg/day, and absolute and relative weights of ovaries were decreased in females given 10 mg/kg/day.

In gross pathology, abnormalities included differently colored foci in animals given 50 mg/kg/day; enlargement, accentuated lobular pattern, and clay coloration of liver in rats given 10 or 50 mg/kg/day; reduced size, discoloration or foci, and/or gelatinous consistency in thymus in animals given 50 or 250 mg/kg/day; reduced spleen size in rats given 50 mg/kg/day; reduced prostate size in males given 50 mg/kg/day; and reduced seminal vesicle size in males given 50 or 250 mg/kg/day.

In histopathology, there were ulceration with minimal to moderate submucosal edema with inflammatory infiltrate and minimal to moderate epithelial hyperplasia in stomach in animals given 50 mg/kg/day, minimal to slight focal to multifocal acute necrosis in liver in an animal given 10 mg/kg/day and in an animal given 250 mg/kg/day, minimal to slight hepatocellular hypertrophy in liver in animals given 10 or 50 mg/kg/day, minimal to massive lymphoid atrophy and minimal to massive multifocal to diffuse congestion/hemorrhage in thymus in animals given 50 or 250 mg/kg/day, minimal to markedly increased number of body macrophages in animals given 10 or 50 mg/kg/day, minimal to marked lymphoid atrophy of spleen in animals given 50 or 250 mg/kg/day, reduced extramedullary hemopoiesis (especially erythropoiesis in spleen in all treated group, and minimal to moderate atrophy of prostate and seminal vesicles in males given 50 or 100 mg/kg/day (seminal vesicles also in males given 10

mg/kg/day).

The investigators concluded a no-observed-effect-level (NOEL) could not be established based on numerous signs of clear toxicity in all treated groups. This conclusion is acceptable. Prominent target organs were liver, thymus, spleen, adrenals, male and female reproductive systems, blood clotting, and platelets.. Signs of neurotoxicity were evident.

e. Twenty Eight-Day Oral Toxicity Study in Rats

This study is consistent with OECD guideline 407, and dose levels were set based on the 14-day study reviewed herein. Five male and 5 female Hsd: Sprague Dawley SD rats per group were given 0 (vehicle control), 0.5, 2.5, or 8.0 mg/kg/day of test substance in distilled water by gavage daily until terminal sacrifice at the end of the 28-day study. Additional groups of 5 males and 5 females per group were similarly treated with 0 or 8.0 mg/kg/day and allowed 14 days of recovery before terminal sacrifice. Animals were 7 weeks old at the start of treatment. Rats were evaluated for survival, clinical signs, body weight, food consumption, functional observational battery, motor activity, hematology, clinical chemistry, urinalysis, gross pathology, organ weights, and histopathology.

All animals survived except for 1 female given 8.0 mg/kg/day which died on study day 28 soon after being bled for blood analyses.

Neurotoxicity was unremarkable except that, on a single occasion, a male given 8.0 mg/kg/day experienced impaired mobility, slight ataxia, and tremors.

Clinical signs were reported as hypoactivity, paleness, cold to touch, difficult breathing, dark urine, and partially closed eyes in the decedent.

Body weights were lower in both sexes given 8.0 mg/kg/day.

In hematology, there were reductions in white blood cell counts and eosinphils and an increase in lymphocytes in males given 8.0 mg/kg/day and a reduction in platelets and an increase in prothrombin time in females given 8.0 mg/kg/day. In treated recovery males, there were decreases in red blood cell counts, hemoglobin, mean red blood cell volume, and mean corpuscular hemoglobin, and in treated recovery females, there were decreases in mean corpuscular hemoglobin concentration and neutrophils and an increase in lymphocytes.

In clinical chemistry, there were increases in chloride in males given 2.5 or 8.0 mg/kg/day, aspartate aminotransferase, gamma glutamyl transferase, and triglycerides in males given 8.0 mg/kg/day, alkaline phosphatase and triglycerides in all treated groups of males (dose response), and potassium, and albumin/globulin ratio in all treated groups of males (no dose response), and there were decreases in creatinine, total protein, albumin, and globulin in males given 2.5 or 8.0 mg/kg/day and calcium in all treated groups of males (dose response).

In clinical chemistry, there were increases in alkaline phosphatase and triglycerides in all treated groups of females (dose response), chloride, sodium, and albumin/globulin ratio in all treated groups of females (no dose response), and aspartate aminotransferase, urea, and potassium in females given 8.0 mg/kg/day, and there were decreases in calcium and globulin in females given 2.5 or 8.0 mg/kg/day and total protein in females given 8.0 mg/kg/day.

Clinical chemistry changes in animals given 8.0 mg/kg/day and terminally sacrificed at the end of treatment were generally found in treated recovery animals. In treated recovery females, alanine aminotransferase instead of aspartate aminotransferase was elevated.

A dose-related increase in urine volume was observed in females given 2.5 or 8.0 mg/kg/day and in treated recovery females. Slight reductions in urinary protein were noted in animals given 8.0 mg/kg/day.

Absolute and relative (organ/body) liver weights were increased in all treated groups, although the increase in relative liver weights in females given 0.5 mg/kg/day was slight, and in both sexes of treated recovery animals. Decreased spleen weights were apparent in all treated groups of females (absolute and relative) and treated recovery females (absolute only). Absolute and relative weights of thymus (males) and spleen (males) and absolute weights of heart (males), ovaries, and adrenals (females) were decreased and relative weights of brain, testes, thyroid, and kidneys (all in males) were increased with 8.0 mg/kg/day treatment. Relative weights of kidneys were also increased in males given 2.5 mg/kg/day. In treated recovery animals, absolute epididymides, spleen, thymus, thyroid, ,and testes weights were decreased, relative thymus weights were decreased, and relative adrenal, brain, epididymides, kidney, and testes weights were increased in males and relative kidney weights were increased in females

In gross pathology, abnormalities included enlargement of liver in both sexes of rats given 2.5 or 8.0 mg/kg/day and a male given 0.5 mg/kg/day and reduced size of thymus and seminal vesicles in animals given 8.0 mg/kg/day. These findings were also noted in treated recovery males.

In histopathology, there were multifocal, moderate hemorrhage, moderate hepatocyte hypertrophy, and single cell apoptosis/necrosis in liver, moderate atrophy of thymus, mild lymphoid depletion in spleen, mineralization in kidney cortico-medullary junction, and acinar cell apoptosis in pancreas in the female decedent. In both sexes given 2.5 or 8.0 mg/kg/day, there were hepatocytic hypertrophy and hepatocytic vacuolation in liver, alveolar macrophage aggregation in lungs, slight to moderate atrophy of thymus (not in females given 2.5 mg/kg/day), and foci of mineralization in papilla or medulla of kidneys (females only). In both sexes given 8.0 mg/kg/day, liver changes also included hepatocytic necrosis and/or single cell apoptosis/necrosis. Colloid depletion in seminal vesicles was observed in males given 8.0 mg/kg/day. Findings in animals given 8.0 mg/kg/day were still noticeable in treated recovery animals.

The investigators concluded a no-observed-effect-level (NOEL) could not be established based on abnormalities in all treated groups. They stated that a toxic effect was seen at the 2 highest dose levels and that results in the 0.5 mg/kg/day group were "...not considered to be adverse, but they were the first step of a dose-related effect which became adverse at the 2 higher dose levels..." Findings in 0.5 mg/kg/day animals included increased liver weights in both sexes, decreased spleen weights in females, and increases in alkaline phosphatase and triglycerides in serum of both sexes and decreased calcium in serum of males. Changes in animals given 0.5 mg/kg/day are consistent with effects in spleen and liver and are dose-related findings in all treated groups. Sensitivity of these organs to test substance effect is further supported by increased severity of effects with increasing dose. At higher dose levels, other organs affected included thymus, male reproductive system, blood clotting, and kidneys. Persistence of numerous effects was evident as results in animals sacrificed at the end of treatment were also found in recovery animals. Conservatively, a NOAEL is not considered established in this study.

f. Ninety-Day Oral Toxicity Study in Rats

This study is consistent with OECD guideline 408, and dose levels were based on the 14-day and 28-day studies reviewed herein.. Ten male and 10 female Hsd: Sprague Dawley SD rats per group were given 0 (vehicle control), 0.03, 0.13, or 0.5 mg/kg/day of test substance in distilled water by gavage daily until terminal sacrifice at the end of the 90-day study. Additional groups of 5 males and 5 females per group were similarly treated with 0 (vehicle control) or 0.5 mg/kg/day and allowed to recover for 8 weeks before terminal sacrifice. Animals were 6-7 weeks old at the start of treatment. Rats were evaluated for survival, clinical signs, body weight, food consumption, functional observational battery, motor activity, ophthalmology, hematology, clinical chemistry, urinalysis, gross pathology, organ weights, and histopathology. Hepatic peroxisome proliferation was assessed by determining cyanide-insensitive palmitoyl-CoA oxidase activity (marker for peroxisomal β-oxidation).

All animals survived.

Expressing palmitoyl-CoA oxidase activity as nanomoles of NADH formed per minute per mg of 3,000 x g supernatant protein, dose-related elevation of this activity in both sexes given 0.13 or 0.5 mg/kg/day with persistence in treated recovery animals occurred as follows (group mean levels):

Dose Level (mg/kg/day)	Males	Females
0	4.37	4.45
0.03	4.80	4.08
0.13	13.49	8.38
0.5	47.94	40.56
0 (recovery)	4.10	3.80
0.5 (recovery)	20.99	20.39

Activity patterns were similar if activity was based on g of liver.

Decreased body weight was apparent in both sexes given 0.5 mg/kg/day beginning on day 64 and continuing throughout the recovery period.

In the counter display test for motor activity, reduced activity was observed in males given 0.13 or 0.5 mg/kg/day (no dose relationship).

In hematology, red blood cell counts, hemoglobin, and hematocrit were lower in males given 0.13 or 0.5 mg/kg/day and mean red blood cell volume and mean corpuscular hemoglobin were higher in males given 0.05 mg/kg/day.

In clinical chemistry, there were : increases in alkaline phosphatase in males given 0.13 or 0.5 mg/kg/day, in treated recovery males and females, and in females given 0.5 mg/kg/day; urea, chloride, and albumin/globulin ratio in males given 0.5 mg/kg/day; triglycerides and albumin/globulin ratio in females given 0.13 or 0.5 mg/kg/day; total protein in females given 0.5 mg/kg/day, increases in urea and inorganic phosphate in treated recovery males; and increased triglycerides, sodium, albumin, and albumin/globulin ratio in treated recovery females : decreases in total bilirubin, creatinine, and globulin in males given 0.5 mg/kg/day, calcium in all treated groups of males (no dose relationship), total protein in males given 0.13 or 0.5 mg/kg/day, total bilirubin in females given 0.5 mg/kg/day, albumin in females given 0.13 or 0.5 mg/kg/day; alanine aminotransferase and globulin in treated recovery females; and sodium in treated recovery males

In urinalysis, specific gravity was decreased in males given 0.5 mg/kg/day.

Absolute adrenal, heart, spleen, and thymus weights were decreased in males given 0.5 mg/kg/day, absolute testes weights were increased in males given 0.13 or 0.5 mg/kg/day, relative (organ/body) brain and kidney weights were increased in males given 0.5 mg/kg/day, absolute and relative kidney weights were increased in females given 0.5 mg/kg/day, and absolute and relative liver weights were increased in males and females given 0.13 or 0.5 mg/kg/day and in treated recovery males and females

In histopathology, there were hepatocellular hypertrophy in liver of both sexes given 0.13 or 0.5 mg/kg/day and in both sexes of treated recovery rats, liver pigmentation in all treated groups of females and treated recovery females and in a male given 0.5 mg/kg/day, hepatocytic necrosis in liver in a female given 0.5 mg/kg/day, increased incidences of spleen pigmentation in all treated groups of females, chronic inflammation, edema, and mucosal ulceration in stomach of males given 0.5 mg/kg/day, thymus pigmentation in males given 0.5 mg/kg/day, increased incidence in hydrometra of uterus in females given 0.5 mg/kg/day, and increased incidence of alveolar foamy macrophages associated with interstitial inflammatory cell infiltrate in lungs of females given 0.13 or 0.5 mg/kg/day and in treated recovery males and females.

Other results were unremarkable.

The investigators concluded 0.03 mg/kg/day as a no-observed-effect level (NOEL) based on various results in clinical chemistry and pathology supporting treatment-related effects at the higher dose levels. This conclusion is acceptable, and 0.03 mg/kg/day is also concluded as a NOAEL herein. At the 2 higher dose levels, target organs for toxicity are indicated by findings in clinical chemistry, organ weights, and histopathology for liver, lung (histopathology) and hematology for the red blood cell system (anemia). At 0.5 mg/kg/day, treatment-related effects were evident on body weight, kidney (organ weights, clinical chemistry), and stomach (histopathology). Changes found in all treated groups were without dose relationship. With respect to pigmentation observed in pathology, toxicologic significance is questionable since incidence in liver was low (1 or 2 females in each dose group) and all 5 treated recovery control females had pigmentation in spleen (4 in each treated group of females had this finding). The pigmentation was reported as yellow-brown, and the investigators stated that lipofuscin-like pigment has been reported occasionally in liver cells of untreated Hsd: Sprague Dawley SD rats and in liver cells of animals treated with different classes of substances including agents which induce peroxisome proliferation.

Evidence for the test substance as a peroxisome proliferator was obtained as clearly increased levels of marker cyanide-insensitive palmitoyl CoA activity in liver of both sexes given 0.13 or 0.5 mg/kg/day.

5. Systemic Toxicity Data and Risk Assessments with PFOA

The toxicology of PFOA is extensively detailed and reviewed in the January 4, 2005 USEPA Draft Risk Assessment of the Potential Human Health Effects Associated with Perfluorooctanoic Acid and Its Salts identified as a review draft for the Science Advisory Board. Since do not quote or cite is stated on this document and since there is no need to rereview these data herein, the overview of systemic toxicity and current oral and inhalation risk quantitative risk assessments described in the SAT report for P08-88 should be adequate to judge its applicability to the systemic toxicity assessment of P08-88.

In the assessment conducted by the state of West Virginia with input from EPA, the RfD for oral exposure was determined to be 0.004 mg/kg/day and the RfC for inhalation exposure was determined to be 1 ug/m3. Some of the key findings for noncancer assessment are for PFOA and/or its salts:
90-day dietary study in male rats - NOAEL = 0.47 mg/kg/day based on liver effects at 1.44 mg/kg/day. The benchmark dose was 1.3 mg/kg/day;
two-generation reproduction study in rats, gavage - LOAEL = 1 mg/kg/day based on increased liver and kidney weights in P and F1 generations;
2-year dietary study in rats - NOAEL = 1.3 mg/kg/day in males based on increased liver weight, hepatic cystoid degeneration, increased ALT enzyme activity, testicular vascular mineralization and LOAEL = 1.6 mg/kg/day in females based on an increase in the incidence of ovarian stromal tubular hyperplasia; the benchmark dose was 0.73 mg/kg/day based on liver effects in males;
26-week oral study in cynomolgus monkeys - LOAEL is from 3 to 10 mg/kg/day based on 30% increased absolute liver weight with no NOAEL;
2-week dermal study in rats - increased liver weight and liver pathology;
2-week inhalation study in male rats - liver effects at 7.6 mg/m3; severe toxicity including the death of one animal at 84 mg/m3, increased lung and testes weight at 84 mg/m3;
inhalation developmental toxicity study in rats - maternal deaths, reduced maternal weights, reduced fetal weights at 25 mg/m3;
oral developmental toxicity in rabbits - increase in skeletal variations at 50 mg/kg. The concern for PFOS is for liver toxicity, liver cancer, thymus effects, reproductive toxicity and developmental toxicity.